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Microchimerism in the human brain

More questions than answers

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Recently, our group reported the presence of microchimerism (Mc) in the human brain by performing quantitative PCR on female human brain tissues to amplify male DNA. We found brain Mc to be relatively frequent in humans and widely distributed in this organ. Our data also suggested a lower prevalence of brain Mc in women without Alzheimer disease than women without neurological disease. Altogether, these findings suggest that Mc could sometimes influence health and disease of the brain. As further research will be required to clarify this issue, here we discuss some of the questions that could be addressed to improve our understanding.

Keywords: microchimerism, brain, Alzheimer disease, pregnancy, blood-brain barrier

Abbreviations: BBB, blood-brain barrier; Mc, microchimerism

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During pregnancy, the fetomaternal exchange of blood gases, nutrients, and wastes via the placenta is necessary to sustain the life of the fetus. These exchanges are directional, as oxygen and nutrients supplied by the mother are received by the fetus in exchange for carbon dioxide and various metabolic wastes that it produces. As much as the placenta is physiologically important, we now know, more than ever, that bidirectional exchange of genetic material and cells occurs between fetus and mother also via the placenta, rendering this filter a biologically and evolutionarily important function.

In humans, years after pregnancy, many anatomical locations have been described to harbor microchimerism (Mc),[1] generally defined as the presence of a small amount of foreign genetic material and/or cells in an individual. The widespread distribution of Mc suggests that virtually any location in the human body may be microchimeric, potentially including areas that are typically considered immune-privileged (e.g., brain and eye). For the brain to harbor Mc may initially seem more unlikely than other locations because of the blood-brain barrier (BBB). However, studies demonstrating Mc in mouse brains[2,3] suggest the same could occur in humans. Indeed, one study[4] offered a glimpse of Mc in the human brain, but it was not until recently that the subject was directly addressed in humans. We conducted a study to investigate the prevalence and concentration of Mc, presumably of fetal origin, in the human female brain.[5] Using real-time quantitative PCR to amplify male DNA in female brain tissues, we studied women without neurological disease or with Alzheimer disease and found that 63% of females tested positive. Results also suggested a lower prevalence of male Mc in women with Alzheimer disease than women without neurological disease. These findings raised many questions about the potential role of brain Mc in health and disease, some of which are discussed in this addendum.

A popular method of detecting Mc has been the amplification of male DNA sequences in females using highly sensitive quantitative PCR assays. As such, the presence of Mc would be presumed of fetal origin because a male birth is the most likely source of male Mc in women. However, detection of foreign HLA-specific sequences[6] is a powerful method to more definitively define the source of Mc. We provided some evidence that

Mc present in a woman's brain could be attributed to a prior fetus she carried,[5] but further evidence is warranted. Although the logistics of specimen collection for performing such an experiment are likely not straightforward and the number of testable subjects limiting, efforts to corroborate the results of male Mc testing with those from HLA-specific Mc testing would avoid ambiguity in result interpretation. More importantly, since HLA-specific or other polymorphism-specific assays are not sex-dependent, Mc from both male and female fetuses can be investigated. Thus, one can determine whether the brain of a woman who had multiple births harbored Mc of more than one fetal source, or whether maternal Mc is present as has been suggested previously.[4]

In past murine studies, Mc investigation often did not specify the region of the brain that was studied.[2,7-9] Where certain regions were tested,[3,10] the number of areas explored was few. Nevertheless, Mc was commonly observed in the olfactory bulb of mice,[3] a structure located in the frontal lobe. Considering our data,[5] we tested for Mc in the frontal lobe of three females, none of which were positive but none could be determined to contain the olfactory bulb. Thus, future investigation of Mc in the human brain should include the olfactory bulb particularly when studying the frontal lobe. If prevalence and concentration of Mc were higher in this structure than others, this could have implications regarding potential mechanisms of immunological tolerance (or immunity) to antigens derived from Mc in the brain. This is because brain antigens can be trafficked into the cervical lymph nodes by crossing the cribriform plate (above the olfactory bulb) to the nasal mucosa for presentation to immune cells.[11]

Finally, women with preeclampsia during pregnancy are thought to have increased cerebral blood flow associated with increased BBB permeability.[12] This should create a unique opportunity for greater trafficking of Mc into the brain. The obvious prediction is that brain Mc would be more prevalent and present at a higher concentration in preeclamptic pregnant women compared with healthy pregnant women. It would be interesting if future studies could test the brains of women who died secondary to complications of preeclampsia for Mc and compare with women who died of other complications during pregnancy (since the brains of otherwise healthy women who died due to pregnancy may be extremely difficult to acquire). Should our hypothesis hold true, it would suggest that other pathophysiological conditions that compromise the BBB could also promote Mc in the brain.

As is often the case, research allows us to reveal a little more of the unknown, but raises even more questions when the dust settles. However, knowing what questions to ask is an important step to begin to further our understanding of biology. We hope that some of the questions discussed are of interest to others and will contribute to ongoing research efforts in this new area of research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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